We've Seen the Future!

POPULAR MECHANICS

HOW YOUR WORLD WORKS

A GUIDE TO URBAN LIFE, 2045

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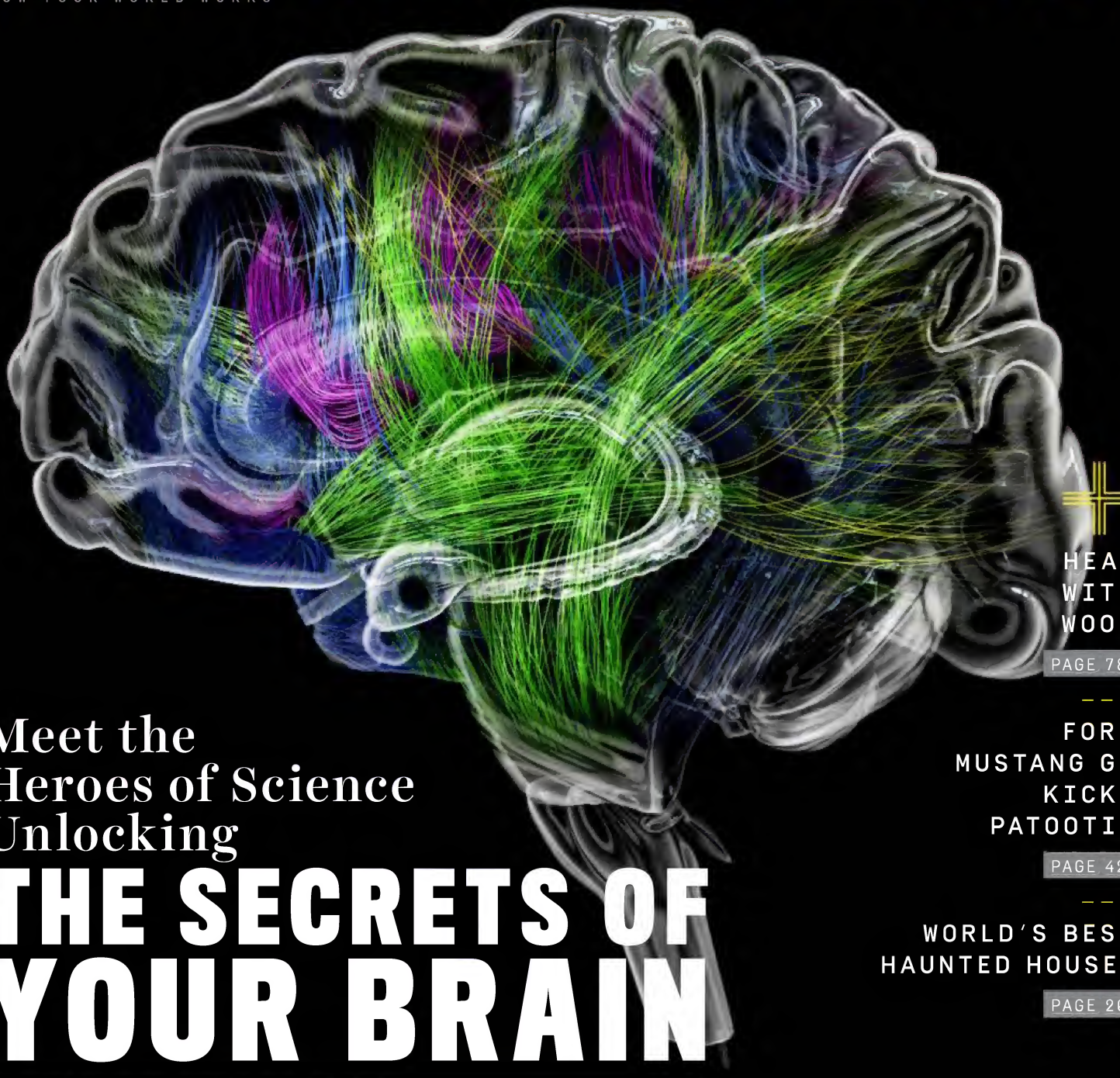

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Meet the Heroes of Science Unlocking

THE SECRETS OF YOUR BRAIN

NEW UNDERSTANDING OF...

How It Really Works | **How To Heal It** | **How To Make It Stronger**

BY JACQUELINE DETWILER

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AMERICA'S MAGAZINE SINCE 1902

Tamara Casper checks the time as a dedicated prep team at the Allen Institute for Brain Science meticulously slices a human sample. The slices will go to a half-dozen research groups.

TRUE STORIES OF INDEFATIGABLE RESEARCHERS, HEROIC ENGINEERS, AND CHAMPIONS OF NEUROSCIENCE WHO ARE FINALLY TURNING THE CORNER IN THE EFFORT TO UNDERSTAND, HEAL, AND IMPROVE THE HUMAN BRAIN.

THE INCREDIBLES

BY JACQUELINE DETWILER
PHOTOGRAPHS BY BRIAN FINKE

THE PRESENT

AL GARDNER and his brother-in-law built the house in Mount Kisco, New York, back in 1984—two stories, three bedrooms, with a sweet little porch overlooking a sunny backyard. At the time, Gardner had worked in construction management for years. He had, in fact, been mechanically inclined ever since he was a kid, when he helped refurbish a Beaver tractor his dad bought from a neighbor. But the house was the first he ever built from scratch, and he was proud of it. Not many people could say they'd built a house for their family these days. Al Gardner could.

Al has a hard time walking up the stairs to his home's second floor these days, so he lives on the first. In a lounge chair, surrounded by pictures of his family and the homes he built, he slowly, carefully crosses one knee at the ankle like he's in a business meeting. His legs are thin and pale and papery. His face, too, has taken on a gauntness since the photo of his daughter's wedding, mounted on the wall right in front of him, was taken back in 2009. Al lunges forward as if he might stand. But then, when he tries to say hello, all that comes out is a guttural moan.

When Al, who is sixty-eight, was diagnosed with progressive supranuclear palsy (PSP) in 2012, he was not guaranteed even this. The disease, caused by degeneration of cells in areas of the brain associated with movement, balance, and thinking, often results in death in about seven years. It has no known cause and no cure. Think of it like Parkinson's disease but faster, and more horrible. L-DOPA, a drug that can reduce symptoms in Parkinson's patients and help them move, usually has no effect on PSP. Apart from an aspirin, an antacid, and something for bladder control, Al doesn't even take any drugs. There aren't any to give him.

Al's wife, Fran, ruffles his hair. He stares straight ahead. Al can no longer blink or move his eyes, which Fran says is the worst of it. He has to wear sunglasses just to go upstairs. For now, Al can still communicate in writing: Last week he had a sinus infection, and hadn't been able to make it out of the house for his usual appointments. On the whiteboard he uses to communicate, he wrote a single word: *bored*.

As the losses mount, Fran has written out an affirmation she can recite when she needs it. She has joined support groups and is active in the PSP community. She smiles as if making the motion is all that's keeping her afloat. "We've been fortunate to have this time," she says, upstairs, in the kitchen, where Al will not hear. "It could be a lot worse."

The Neuroscientist Who Wants to Turn Support Cells into Neurons

WASHINGTON, D.C.

A DISHEVELED GUEST emerges from the elevator of the Washington Plaza Hotel in Washington, D.C., carrying a bag of laundry to drop off at the front desk. He looks out the window, where a giant picture of a brain lumbers past on the side of a city bus.

"Are you here for the neuroscience conference?" the man asks a stranger standing next to him. The bus departs, revealing packs of neuroscientists making their way around Thomas Circle, black poster tubes for presentations slung across their shoulders like quivers. "It just seems like everyone is here for this thing," the man says. "I'm just trying to figure out how far it goes."

Far. This weekend marks the beginning of the Society for Neuroscience's annual meeting, which attracts more than thirty thousand professors, doctors, graduate students, and postdoctoral researchers from more than eighty countries to discuss the future of the human brain. SfN, as the conference is called, is so enormous that only seven cities in the United States can even accommodate it.

Inside the Walter E. Washington Convention Center, the featured lectures have already begun in the auditorium, which is so capacious (and dark) you could play a game of Marco Polo in it with your eyes open. Up next is Magdalena Götz, a professor who has flown in from Ludwig Maximilian University of Munich to give a talk about treating brain injuries in mice. Her face, complete with blunt, Germanic bangs, is briefly duplicated on a giant screen like an evangelical preacher's.

There are many reasons that progressive supranuclear palsy, the disease Al Gardner has, is hell on earth, but they can all be traced to one: Generally speaking, neurons don't grow back. With a few exceptions, when the brain's primary information-processing cells die, they're dead. So today, when a doctor encounters a neurodegenerative disease or a brain injury, the strategies are limited: one, do your best to keep the rest of the neurons alive; and two, encourage the brain to work around any sections that are damaged. If someone could persuade neurons in human patients to spontaneously regenerate, it would be one of the most incredible achievements in neuroscience. For now, it remains impossible.

Götz doesn't study neurons. Or, at least, not at first. She works on another type of cell, called glia. Glia (Greek for "glue") comprise at least half of the cells in the brain, but scientists thought they were just a supporting framework for neurons for more than a century. Then, in 1990, a Stanford researcher named Stephen J. Smith discovered that a particular type of glia, star-shaped cells called astrocytes, could communicate with each other. It

started a race to figure out what these strange cells did. The list keeps growing.

"When an injury strikes, astrocytes become activated," says Götz. They can kill more neurons, or they can help keep them alive. They can regulate inflammation and control how neurons reconnect after their networks have been decimated. Some stick around and form a scar. Astrocytes are important all the time, but after a brain injury, the scaffolding runs the asylum.

Here's why any of this matters: By injecting certain proteins (called transcription factors) involved in development directly into the brain, Götz and her team in Munich have figured out how to alter the function of astrocytes after an injury. Like *really* alter it. Instead of building useless scar tissue, Götz's astrocytes transform into brand-new neurons to replace the ones that were lost. Götz has done this to human cells in a dish, and she's done it in living mice. Her team has even convinced the reprogrammed neurons to send little feeler projections out to the places they should go. Now, nearly a year after her talk in Washington, D.C., she has partnered on a review article with a doctor who sees Parkinson's patients and is working on ways to deliver the transcription factors to mice through oral drugs rather than brain injections.

"Predictions about how long something will take [to be available for humans] are notoriously wrong," Götz says. "This is how much I can say: We did this for the first time in a living animal in 2005 and that was considered a complete blue-sky approach. Only fifteen years later we've reached a stage where clinicians are interested." That doesn't mean that fifteen years from now doctors will be able to prescribe a course of transcription factors to cure PSP. But then again…

THE JOHNS HOPKINS TEAM WANTS TO REPLACE HOSPITAL DRUDGERY WITH **FAMILY GAMES OF VIRTUAL SHARK WAR.**

The auditorium is only about half full for Götz's talk, which seems incredible when you consider the potential impact of her work. Reprogramming support cells to cure brain disease! But SfN is hosting thousands of presentations over the next five days. It's a halcyon Saturday in Washington, D.C. And in neuroscience, amazing things are happening everywhere you look.

Nick Dee and Herman Tung, two other members of the Allen Institute's tissue processing team, use a vibratome to slice the human brain sample.

The Philanthropist Who Wants to Figure Out How the Brain Works

SEATTLE

THE YELLOW-BRICK HARBORVIEW Medical Center, decorated in places with white chevrons and pocked with dollhouse windows, is a gorgeous building, an early-twentieth-century sanitarium overlooking Seattle's infinite harbor. But inside the basement, it looks much like any other hospital—a labyrinth of tiled corridors broken only by the occasional set of double doors. Outside one such set, under a red banner that reads "Operating Room Staff Only," a research associate named Tamara Casper leans on a black industrial kitchen cart, waiting. For forty-five minutes, she was waiting in a lab down the hall, but now she's moved here to wait some more.

Past the double doors, Jeffrey Ojemann, a brain surgeon from a family of them (his father, uncle, and brother are neurosurgeons, and his mother is a neurologist), stands over the exposed cerebral cortex of a twenty-three-year-old woman whose epilepsy has become unmanageable. It's likely that the woman is awake: Ojemann often wakes up patients at this point in the procedure, to apply electrical current to the brain while the patient names pictures. He wouldn't want to accidentally remove an irreplaceable chunk of neurons on his way to the knob of tissue that has been causing the woman's seizures—a spot known as an epileptic focus.

Ojemann makes a cut in the side of

the woman's temporal lobe, which is above the ear, avoiding what's known as the eloquent cortex, parts of the brain that are generally understood to allow people to move, hear, speak, and see. He tunnels in to reach the focus. He will do his best to remove as little as possible.

About twenty minutes later, a young woman wearing dark blue scrubs with a mask drawn down around her neck emerges from the double doors with a lurid pink and white marble in a jar. It's the manhole cover Ojemann cut from the outer layers of the woman's brain to get down to the epileptic focus. The marble is healthy, normal brain tissue. Unfortunately, once it was severed from the neurons surrounding it, there was no putting it back. "Sorry it took a little while," the woman says, handing over the jar. "But it's literally brain surgery."

Tamara Casper places the jar in a Styrofoam cooler packed with ice and rolls her cart out into the street. She loads it into the back of an anonymous white courier van, which slips into Seattle's afternoon traffic. Within fifteen minutes, the marble has been received at the Allen Institute for Brain Science—founded by eccentric Microsoft cofounder and Seattle-based philanthropist Paul Allen—where it will become a permanent part of the first-ever cellular map of the human brain.

Many people think that because neurosurgeons are able to operate on the brain, there must already be a map of how it works, and that is true, to an extent. A structural diagram of the brain has existed since the early 1900s, outlining the regions where cells appear different under a microscope. But most of what doctors know about the function of each of those pieces comes from presurgical electrical recordings, like the ones Ojemann takes; or functional magnetic resonance imaging (fMRI) studies, which show how blood flow changes while people do tasks; as well as from a whole lot of doctors accidentally removing parts they shouldn't. There is still a lot of empty space on the map. Especially when compared to the rest of the human body, the brain is virtually uncharted.

In 2003, Paul Allen learned that his mother had Alzheimer's disease. Already obsessed with computers, and determined to donate most of his fortune to charity, he became fascinated with the brain, earmarking an initial $100 million to found an institute that could do the comprehensive, labor-intensive work that would be required to figure out how it works. It would be like Great Britain's Royal Geographical Society—the world's first shared observatory for brains.

Over the years, the Allen Institute has used mice and the brains of cadavers to create atlases of where various genes are expressed in the brain. They've mapped the spinal cord. They've mapped primate brains. In accordance with Allen's instructions, all of the diagrams and data are available to the entire neuroscience community for free. But even that hasn't been enough to explain how an organ can process information. Eventually, the Allen Institute's staff started to wonder if developing a periodic table of brain cells would help researchers figure it out. Just how many different kinds were there?

The short answer: probably more than a thousand. Since 2015, the institute has been working on the first-ever taxonomy of brain cells, sorting them by their electrical activity, the genes they express, and their morphology (how they look). They started with living cells from mouse brains, which are easier to get, but have recently moved over to humans, partnering with six local doctors to pick up leftover cells from surgeries that would otherwise be thrown away or maintained in hospital tissue banks.

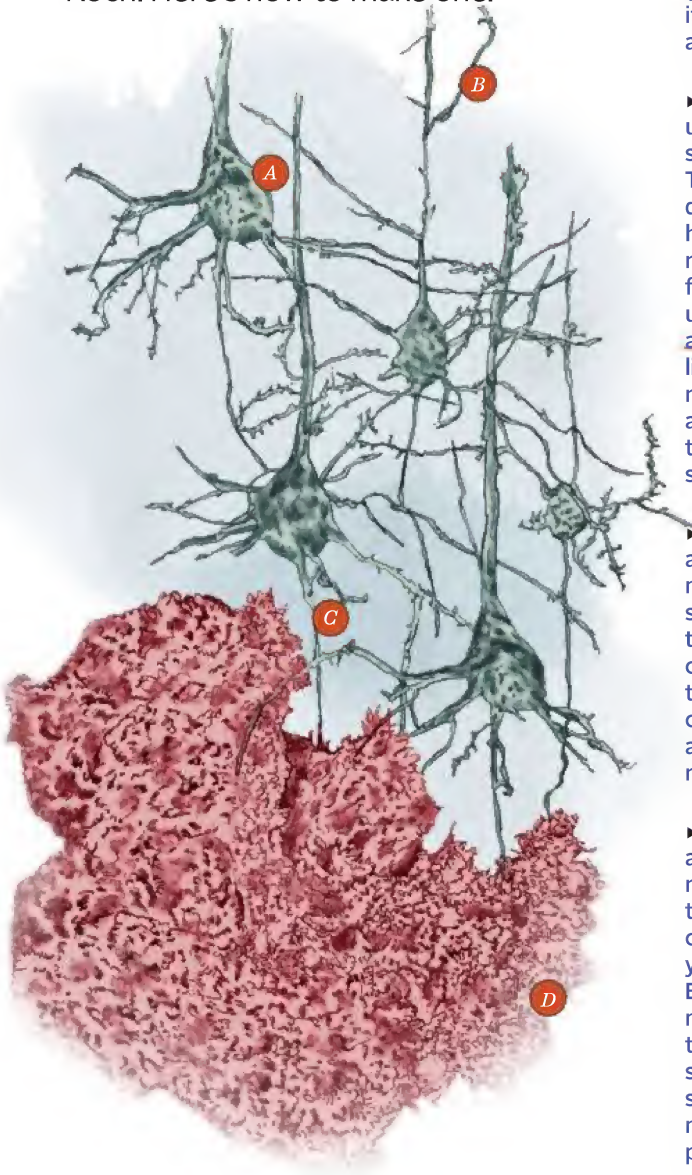
Researchers at the Allen Institute in Seattle are using precious samples of human brain tissue, like these taken from the cerebral cortex, to create a kind of periodic table of all the cells in the brain.

Christof Koch, the Allen Institute's chief scientist and president, compares the work to mapping the genome, which has radically transformed medicine since it was completed in 2003. "Today, nothing in biology makes sense anymore without knowing the involvement of genes," he says. "The same thing is true of cell types. It is going to be an absolute, necessary next step to understand who we are."

After the sample Tamara Casper collected from Harborview Medical Center arrives at the Allen Institute in the white courier van, she and a team of technicians meticulously slice it and hand it off to researchers who will probe the cells within before they die, which can take anywhere from several hours to three days at the outside. It's an all-hands-on-deck situation. Some of the staff will remain

HOW TO BUILD A BRAIN

"The brain is the most complex structure in the known universe," says Allen Institute chief scientific officer Christof Koch. Here's how to make one.



▸ First, procure roughly 86 billion neurons (A), which are cells that collect information from other cells, via projections that look like tree branches (dendrites [B]) and shoot that information down itty-bitty cattle prods (axons [C]) using electricity generated by sodium and potassium ions.

▸ Next, get some as yet unknown number of support cells called glia. These include oligodendrocytes, which wrap the highways of the longest, most important axons in fatty sheaths to speed up their electrical signals; astrocytes (D), which look like sponges and can communicate with each other; and microglia, which act as the brain's private immune system.

▸ Each neuron should have an average of 7,000 connections, mostly through synapses, empty space that must be crossed by chemicals. There are more than 100 of these chemicals (neurotransmitters) and many neurons release more than one.

▸ All of your neurons and glia and other bits must self-assemble, and their connections should change based on what your brain encounters. Every single time your new brain does something it remembers later, such as reading this story, some parts of the network have to change permanently. Good luck!

Already, the crew has completed an early prototype, and it is incredible, like the first map scribbled by a team of conquistadors returning from South America. Click on one neuron and the software zooms in, showing you everything it is connected to and how. Astrocytes, it turns out, actually look more like sea sponges than pointed stars. Neurons called chandelier cells connect axon to axon, which is weird. Pyramidal cells shoot one thick dendrite up to the brain's surface, like a periscope. Looking at it, you can see a future in which the cell census, combined with an interactive mapping tool like this, could lead to the kinds of science-fiction tools curing brain diseases will require—cellular surgery, remapping the cortex, even rewiring a damaged brain using Götz's astrocyte-neurons.

The name of this second project is MICrONS, short for Machine Intelligence from Cortical Networks, and, in addition to Paul Allen's generous grant, it is supported by $18.7 million from IARPA, the U.S. intelligence agencies' high-risk, high-reward research program. It is also working with machine-learning researchers from Google. Certainly, IARPA and Google find the medical applications of MICrONS compelling, but their primary interest is in reverse engineering the brain's information-processing setup to develop ever more powerful machine-learning algorithms. These could, in turn, help the Allen Institute decode more complex strategies the brain uses to process information, forming a feedback loop of computational progress that either ends in an exhaustive characterization of human intelligence and the end of brain disease…

Or the rise of sentient death machines, depending.

at the center until one or two in the morning, painstakingly selecting cells that look hardy and poking them with vanishingly tiny glass pipettes to zap them with electricity and record their response. Thankfully for the technicians who perform this work, human cell samples aren't an everyday occurrence. The Allen Institute's partnerships net them only about forty a year, each of which is portioned for a half-dozen teams.

But even during the human sample frenzy, the cell census is not the only ambitious project underway at the Allen Institute. On the first floor, a group known as the electron microscopy team is disassembling a cubic millimeter of mouse brain (the size of a grain of sand) into twenty-five thousand slices, taking 250 million microscopic photographs of those slices, and then reassembling the photos into an interactive Google Earth–style street view that will allow researchers to trace a billion connections between roughly a hundred thousand neurons.

The Video-Game Designers Who Want to Improve Stroke Care

BALTIMORE

IT IS IMPOSSIBLE to eat the darn fish. I rock my right hand forward and backward and the dolphin on the screen, mimicking me by way of a hacked Xbox Kinect, halfheartedly starts forward and then flops over on its back. I swing my forearm around in a circle, which makes it swim away from me, but upside down, in a way no real dolphin would deign to move. Finally, by undulating my shoulder like I'm playing an octopus in a modern dance piece, I manage to get the dolphin to swim up to a fish, open his mouth, and chomp it. And this is as easy as this game gets.

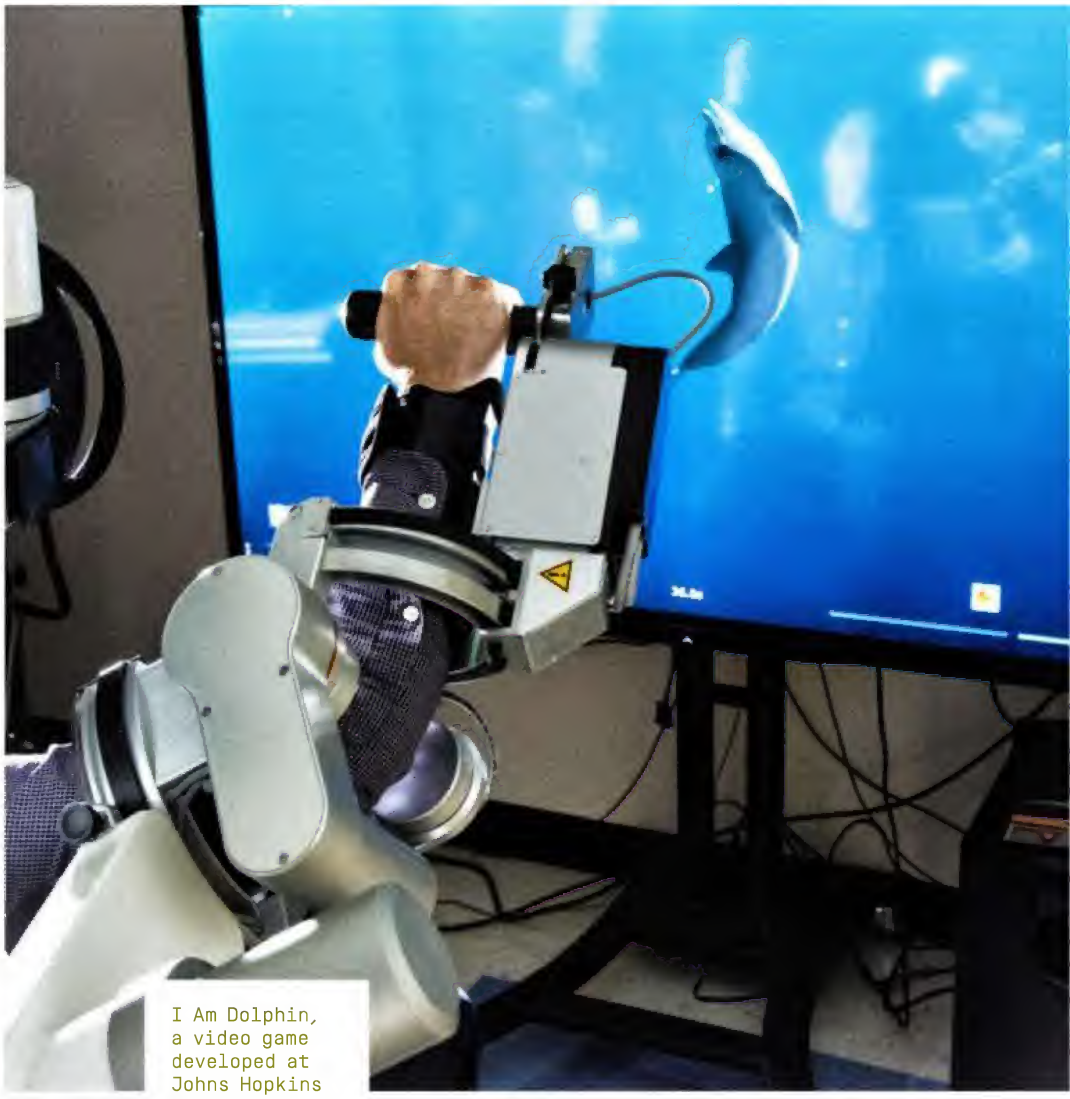
"There's about 110 levels in here," says Promit Roy, the bespectacled software architect who built this game from scratch on a programming engine he also built from scratch. "As you start to get up there, the fish get faster and smarter. And there are sharks."

Sharks?

"They're going to start to attack you."

Roy, who used to work for Microsoft and Nvidia and helped ship the game Fracture for Xbox 360 and PlayStation 3, is one of three founding members of the Kata Design Studio at Johns Hopkins Stroke Center in Baltimore. Along with Omar Ahmad, who has a Ph.D. in computer science, and John Krakauer, director of the Brain, Learning, Animation, and Movement Lab at the Johns Hopkins University School of Medicine, he has created one of the most advanced therapeutic video games in the world.

While the neuroscience community painstakingly researches treatments that may be able to physically repair brain injuries and neurodegenerative diseases, most current therapy encourages the brain to rewire itself after it has been damaged, which can be remarkably effective. But it takes time, and an enormous amount of effort. Overall, rehabilitation is a devastatingly boring affair. "There is severe depression across much of the patient population. There's the question of: Do you even want to do your therapy? No one wants to do their therapy," says Roy. Many patients register the particulars of their biological catastrophe—the alarming brain scans, the bleak recovery timelines—and then mentally check out.



I Am Dolphin, a video game developed at Johns Hopkins University School of Medicine, retrains stroke patients to move their arms. The machine above helps counteract gravity.

Roy, Ahmad, and Krakauer identified the main problem as one of motivation. If patients believed they were doomed to a life of approximations—of struggling to lift a cup to their face over and over again, which is what some patients do in occupational therapy—why would they invest the effort required to recover to the best of their ability? What stroke patients needed was a trick—a therapy so entertaining that they would do it until they beat it, no matter how hard it was, or how long it took.

"They're told *eat the fish*. That's the only instruction they get," says Roy, demonstrating the first round of the game the team eventually created. Called I Am Dolphin, it allows the patient to inhabit a sea creature named Bandit, moving and twisting the damaged side of her body (stroke is a disruption of blood flow that often affects just one side of the brain, causing difficulty moving the opposite side of the body) to make the dolphin flip and glide. "I don't know how a dolphin moves if I'm coming into this. I don't know what I'm supposed to do. So I have to figure it out," says Roy. "I'm not thinking about my disability. I'm not thinking about the fact that I'm in a hospital. It's just: How do I eat these guys?"

Something about relearning to move this way—by pretending to be a cartoon that isn't restricted to moving in standard, human ways—is extremely effective in helping stroke patients recover. Kata's pilot patient, a man named David Stevenson, was paralyzed in his left arm and leg by a stroke a few years ago at the age of just forty-seven. After playing I Am Dolphin using an additional gravity-assistance system, he left with movement quality in his arm that was practically indistinguishable from that of a person who had never had a brain injury. Although the team is still analyzing the data from their first fully enrolled study, preliminary results suggest that an intense regimen using the dolphin game is significantly more effective than traditional methods of therapy.

Jarreau Wimberly, an illustrator and graphic designer given to whimsical ties and mismatched prints, recently joined the Kata team after fifteen years of drawing illustrations for places like Marvel, Hasbro, and Blizzard. Now, his illustrator's touchscreen is covered in mock-ups of Mad Max–style aquatic space arenas, squids with tentacle fists, and a tiny goldfish driving a robot great white. He adores his new gig—instead of toiling away at some task in a private-industry product pipeline, he's actively designing I Am Dolphin 2.0, which is likely to include a multiplayer aquatic soccer extravaganza that could allow recovering stroke patients to play with their friends and family when they come in on visits.

Imagine: the long-term hospital slog transformed into a family game of Wii dolphin. Virtual touch football with laser sharks. Stroke patients believing that—if they apply every ounce of their energy to a goal—there is still something they can win. The increase in joy alone could explain why the game has been so effective.

Toward the end of the demonstration, Roy shows me an

Jarreau Wimberly designs video games that can retrain stroke victims to move their limbs. He wants to make the games as entertaining as possible.

advanced level of I Am Dolphin, one that a patient would reach only after weeks of dedicated practice. Waves of angry fish and sharks swarm Bandit to the sounds of heavy drums. To escape them, the dolphin can attack, he can swim away, or, as one patient figured out, he can flip out of the water into the night sky, soaring end over end in the moonlight. The stage is berserk, high-flying, as tough as a video game a healthy teenager might fail and curse at.

"I honestly don't know if I can beat this," says the man who built this game from nothing. "But patients can."

The Biophysicist Who Wants to Unravel a Problem Protein

NEW YORK CITY

BEFORE ANTHONY FITZPATRICK enters this story with his super microscope, it is first important to know a strange fact about neurodegenerative diseases. Most of them—including PSP, Parkinson's, Huntington's, Alzheimer's, Pick's disease, fronto-temporal dementia, amyotrophic lateral sclerosis (ALS), and chronic traumatic encephalopathy (CTE, the post-concussive disorder that strikes NFL players and boxers), among others—involve proteins in the brain folding themselves into clumps.

No one knows why this happens, or how it gets started, or even whether the proteins cause the diseases or are a side effect of something else that does, but the phenomenon shows up often enough that it clearly means *something.* In Parkinson's disease, a protein called alpha-synuclein origamis itself into a mess. In other diseases, it's a protein called amyloid-beta, or one called tau. Regardless of the protein's name and normal function, the outcome is the same: a brain riddled with tangles of useless proteins.

In contrast to many other neurodegenerative diseases, Alzheimer's disease shows up in the brain as two misfolded proteins, which makes it one of the more complicated diseases to fight, at least on a molecular level. If you've heard doctors talk about "plaques and tangles" in reference to Alzheimer's disease, this is what they mean: The plaques are made of a misfolded protein called amyloid-beta. The tangles are tau.

In the early 1990s, drugmakers seized on amyloid-beta as the main target for Alzheimer's drugs, because it could cause problems if it started folding itself all screwy elsewhere in the body (in the heart, for example), and because genes that coded for amyloid-beta were mutated in patients who had family histories of Alzheimer's. Amyloid-beta also appears to start degenerating before tau, which made drug developers think that if you stopped it, you could halt the disease entirely.

For the next twenty-five years, pharmaceutical companies targeted misfolded amyloid-beta with more than two hundred drugs. Nearly all failed. So many amyloid-beta drugs failed, in fact, that most of Big Pharma has quit developing drugs for Alzheimer's disease altogether, ceding the market to smaller, nimbler startups, such as Denali and Aquinnah, with newer ideas. In January, Pfizer pulled its entire neuroscience division, setting aside $150 million instead to fund startups. "I don't think it means that these companies are going to stay out forever," says Cara Altimus, associate director at the Milken Institute's Center for Strategic Philanthropy. "It's that they don't see a pathway today to run a drug through the Food and Drug Administration." (At press time, an amyloid-based drug from Biogen and Japan-based company Eisai called BAN2401 had managed to significantly reduce amyloid levels and slow cognitive decline by 30 percent in a Phase 2 trial.)

So now: Anthony Fitzpatrick. An English biophysicist at Columbia University's new interdisciplinary Zuckerman Institute in New York City, he has the ideal background to sort out the question of protein misfolding. He works with an electron microscope, which is the machine that makes

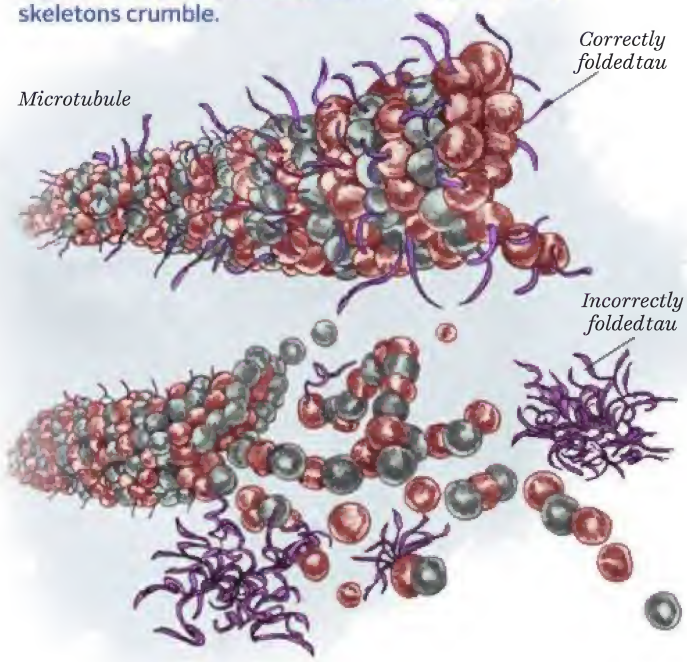
WHAT ABOUT DEPRESSION?

▸ Researchers have known for some time that an episode of depression, even early in life, doubles the risk of developing dementia, but they are just now figuring out how the two diseases fit together. In recent studies, people who had had a bout of depression had more proteins associated with vascular disease and fewer proteins associated with general cell health in their blood than people who never had the disease. "It almost looked like they had premature molecular aging," says Meryl Butters, associate professor of psychiatry at the University of Pittsburgh School of Medicine. Preventing the increased risk may come down to ameliorating the effects of the stress hormone cortisol, which shoots up during depression. *—Sunny Kim*

The Tao of Tau

Behind the protein that's behind nine neurodegenerative diseases.

▸ Tau normally folds in such a way that its ends dislike each other, which helps it stabilize microtubules, the skeletons of axons. When it misfolds, the ends stick together like poorly handled tape. Unsupported, the skeletons crumble.



those pictures of bacteria blown up as big as cheese curls from high school textbooks. In short, he freezes misfolded proteins, takes pictures of them from multiple angles, then uses computers and his own formidable knowledge of chemistry to figure out exactly how they're folded, and why, and how they could be targeted with drugs. Recently, Fitzpatrick achieved a huge coup for Alzheimer's disease research: He became the first person to freeze a protein that came directly from the brain of a woman who died from the disorder and map its structure. Only he didn't start with amyloid-beta. He started with tau.

Fitzpatrick flips his computer around to show me his work, the multicolored loops and squiggles forming a shape like the symbol for Pisces. When tau folds correctly, it joins other tau proteins to support the long hollow cylinders that function as skeletons for the axons of neurons. When it doesn't, it makes a mess like this, and is frighteningly adept at convincing other tau proteins to join it.

Here's the interesting thing about tau: The latest research shows that the spread of misfolded tau, not amyloid-beta, more closely correlates with cognitive deficits in Alzheimer's disease. Maybe amyloid-beta gets the process going, goes the most recent theory, but it's tau that goes around murdering neurons. Tau is certainly capable of doing it all by itself in other disorders. PSP, the disease Al Gardner has, is associated with the buildup of tau in the brain stem, frontal lobes, and basal ganglia. It's considered a "pure tauopathy," one of the first Fitzpatrick believes his research could cure.

The question Fitzpatrick would most like to answer is whether tau is the same protein in all the diseases where it appears, because it might not be. "You have six different forms of the tau molecule that are slightly different length and slightly different behavior," he says. There are at least nine different tauopathies. Some combination of tau type and the type of cell it accumulates in could explain why the various neurodegenerative diseases have different symptoms. Already, the tau Fitzpatrick isolated from the Alzheimer's brain was folded differently than tau that has been studied in labs before. Is the difference between Alzheimer's disease, PSP, and CTE as simple as which type of tau goes bad? If you unlock one disease, can you get all of them?

The only way to find out is for someone like Fitzpatrick to map misfolded tau from brains of people who've succumbed to various brain diseases and find out if they are different on a molecular level. This is why Fitzpatrick has a brain with CTE sitting in a fridge down the hall. He's been trying to crack its code for weeks.

"So far, it looks different," he says.

The Engineer Who Wants to Build Better Brain Interface Devices

CAMBRIDGE, MASSACHUSETTS

ONE REASON IT'S SO DIFFICULT to report a story like this is that, with tens of thousands of neuroscientists all specializing in their own microfields and trying to make a difference as if their very own lives depended on it, the cornucopia of potentially promising treatments is boundless. By the time neuroscientists figure out how the brain works, and why it goes wrong, and how to fix it when it is injured or diseased, they'll have their choice of methods for delivering solutions. One of those methods will be the fibers Polina Anikeeva has made.

Five foot three and compact as a gazelle, Anikeeva is a marathon runner, a rock climber, and one heck of a scientist. She was born to a pair of mechanical engineers in the former Soviet Union, where she so excelled at academics that she was moved to an elite high school, then majored in physics in college. After stints at Cold Spring Harbor Laboratory, the Swiss Federal Institute of Technology in Zurich, Switzerland, and Los Alamos National Laboratory, she got a Ph.D. (at MIT) in a field called optoelectronics, where she worked on a light-emitting nanomaterial technology called quantum dots that was licensed to a startup that was later bought by Samsung. Also: She has a habit of barreling down the halls like a tiny cruise missile, fluttering the flyers on the bulletin boards. You almost want to flatten yourself against the wall.

Unsurprisingly, after five and a half years of studying nano-optoelectronics, light-emitting quantum dots started to bore Anikeeva. Improvements in the field came slowly and incrementally, while she wanted to invent fantastical things that didn't exist. There were few scientific areas where that was a possibility anymore. Neuroscience, though, was a field in its toddlerhood, where it was still possible for a scientist to do big, exciting work. So Anikeeva secured a two-year postdoc in a neuroscience lab at Stanford. She started to think about opening her own lab.

And then: On a climb in California, one of Anikeeva's friends fell fifty-two feet and severed her lower spinal cord. She was left with minimal innervation on one side of her body. The doctors had to bolt a couple of her vertebrae together with giant titanium screws.

"They weren't even doing any kind of functional stimulation or trying to reconnect any of the nerves," Anikeeva says of her friend's treatment. Therapy went the same way it always does: physical rehab, occupational rehab, sit and watch and wait. It seemed to Anikeeva, who had spent years perfecting semiconducting nanocrystals that were being used in television

MIT materials scientist Polina Anikeeva next to the 12-foot tower that draws her preforms into cables that could interface with the brain.

displays, like we should be able to do better for someone who was fighting to walk again.

After Anikeeva saw a brain-stimulation device, which she found barbaric, she knew how she could help. Brain stimulation, which has been used as a therapy for pain and motor disorders since the 1970s, has vastly improved over the last few decades, most notably with the addition of feedback mechanisms that train the systems algorithmically. But the interface is still awful: With every heartbeat, the brain, which has the consistency of pudding, moves in the skull. Sticking a metal wire into it is basically like continuously scraping it with a knife.

And so Anikeeva became determined to design flexible fibers that could interface with the nervous system without damaging it, transmitting signals to reconnect nerves or stimulate neurons. Her latest piece of equipment includes a conductive wire that can send electricity; a tiny tube that can move liquid drugs or chemicals; and a reflective duct that can transmit light, the basis of a new field called optogenetics, which involves genetically alter-

ing groups of neurons so that they can be turned on and off using photons.

Creating a miniature pipeline out of a material that has all of these properties is incredibly difficult. So Anikeeva and her team built biological telecom cables, bundles of separate channels (for light, fluid, and electricity) surrounded by a clear composite. They also built them huge—plastic paperweights the size of a fist with the channels glittering in the middle. To turn these into cables, she heats up the paperweight (called a preform), attaches a weight to it, and draws it out like Play-Doh pasta until it gets thin enough. "The whole thing will become the size of your hair," she says. "But inside they will have the same cross section." She has even devised a water-soluble coating that will temporarily stiffen the fibers so that they can be implanted into the correct location.

In the future, Anikeeva's fibers could become a platform for devices that provide hyperspecific brain therapies. Already, Anikeeva's colleagues at the University of Washington are testing them on mouse models of spinal cord injury. Fibers like Anikeeva's could even connect computational interfaces that would be the brain's version of the artificial heart valve—for example, a fake set of basal ganglia that could operate a Parkinson's patient's body for her. "From a technical perspective, I could make this available right now," she says. But much more remains to be done: due diligence on safety, the improvement of algorithms that can approximate neural activity, and, in many cases, knowing what needs to be fixed in the first place. Optimistically, Anikeeva says, it will be a decade before her fibers can help patients.

Anikeeva usually has a box of samples on her desk to show to visitors, but today it is in front of Congress to convince lawmakers of the benefits of government funding for science. What remain are the preforms that failed, about ten twisted hunks of plastic that are too fat or too short or uneven or broken and had to be stopped in the middle of spooling. They narrow as they rise into wispy tails, like pointy smokestacks.

Anikeeva's climbing friend had a miraculous recovery, by the way. She came to Anikeeva's lab three years after her injury—on foot—to give an inspirational talk to the staff.

At Walter Reed, hospitalman Luke E. Wielechowski demonstrates the MEG, a machine that can track how different parts of the brain communicate in real time as a patient performs tasks.

The Doctors Who Want to Help Soldiers Returning from the Middle East

BETHESDA, MARYLAND

PAST THE WELL-DEFENDED GATES of Walter Reed National Military Medical Center in Bethesda, Maryland, the National Intrepid Center of Excellence (NICoE) rises peaceful and monolithic out of a broad, steaming lawn, like a neoclassical artists' colony. In a way, that's what it is. NICoE, paid for by donations to the Intrepid Fallen Heroes Fund, was designed to offer a soothing respite to the people who visit. The entire staff whispers as they walk through the corridors.

"Eighty-some percent of the people injured in the overseas conflicts in the last fifteen years have been injured through explosive devices," says Louis French, NICoE's deputy director

for operations, at a table in his office. "The sad reality is, if you're close to something that blows up, you can quite literally get hurt head to toe."

It's the head, in particular, that's the problem. Traumatic brain injury has been called the signature casualty of the wars in Iraq and Afghanistan: When a service member is struck by an improvised explosive device, the blast can twist or stretch the axons that neurons use to send information to each other in ways that aren't necessarily visible on an MRI. Many soldiers experience inexplicable neurological or psychiatric problems that continue when they return home. A congressional mandate in 2007 insisted that these people deserved a place that would research their conditions and provide additional treatment. That place is NICoE.

French, along with his colleague, neurologist and chief innovations officer Thomas DeGraba, both wear American flag pins on their lapels. They are very proud of what NICoE is able to provide to service members—a holistic recovery program that extends to the patient's immediate family. But they are also both very honest about what is currently possible in the realm of brain injuries. "We treat symptoms right now," says French, his voice carrying all the heaviness that statement suggests.

Even though neurons themselves do not spontaneously regenerate, training the brain to compensate for deficits works, as the Kata team at Johns Hopkins has proved. Down the road in Bethesda, NICoE is doing something similar: In its signature treatment, a four-week outpatient program, patients receive an initial assessment, then a curriculum of therapy so intense it rivals a camp schedule. There are neurofeedback experts, physical therapists, neurologists, psychiatrists, art and music therapy, acupuncture. There's an immersive 3D treadmill environment the size of a swimming pool that can retrain motion sensitivity and visual integration. Overall, 71 percent of patients who go through the program report an improvement in their quality of life, and that's among the subset of patients who end up at Walter Reed, which generally includes the most challenging cases.

Still, DeGraba says, if he could have one tool that would make his job easier, it would be a way to reveal exactly which circuits have been scrambled by explosive devices in each patient. Most times, people come to NICoE with some subtly warped behavior that could be caused by several different physical problems. Is it psychological? Is it neurological? Is it damage to the visual or auditory system? How do you repair an organ when you can't see what's wrong with it?

MEG, which is short for magnetoencephalograph, is the closest thing DeGraba has to his dream machine. It looks like a cross between a Pixar robot and a beauty salon hair dryer, hulking shyly behind an 11-inch-thick magnetically shielded door. One of just nine such machines in clinical use in the United States, it works by measuring the microscopic magnetic fields that are created as electrical impulses travel down axons. The MEG does this in real, millisecond, thinking-speed time, using sensors supercooled by liquid helium. DeGraba is understandably proud of it.

"It's a game changer for neurologists," he says. "Up until this point, all we had to look at brain-wave activity in a noninvasive way was to put electrodes on people's scalps." MEG, in contrast, can map the whole brain's activity, showing how areas associated with emotion and language and vision and movement communicate with each other in real time as patients perform tasks.

In his office, DeGraba pulls up a set of slides to show me what this means for patients. A few years ago, a soldier came back from the Middle East with a traumatic brain injury from a mortar blast that left him unable to perform his duties. The problem, in particular, was making decisions based on written communications. It sure looked like an executive functioning issue, which could result from damage to the front of the brain.

DeGraba hits play on the slide, and waves of activity sweep across the side of the man's brain. Compared to a normal example, it's as clear as day—a delay and decrease in signal between two areas known to affect the visual processing of words. As it turned out, the man didn't have a problem with executive function at all. His injury had disrupted his brain's processing of letters. He couldn't read quickly enough to make decisions. The soldier was assigned to an incremental program that would help him relearn, starting with just minutes a day. Within a few months, the man got better.

DeGraba had done the impossible: He had looked inside a living person's brain and seen where and how its exceedingly intricate circuitry was misfiring.

And then he had fixed it.

DEGRABA HAD DONE THE IMPOSSIBLE: HE HAD LOOKED INSIDE A LIVING PERSON'S BRAIN AND SEEN WHERE IT WAS MISFIRING. AND THEN HE HAD FIXED IT.

The Future

HOLDING A HUMAN BRAIN is not like holding any other body part. Anyone who has spent time in a biology lab understands the responsibility of working on a formerly living being. But the brain is different. It's more. Holding a brain is the closest you can get to holding a person's soul. If you're the kind of person inclined to such feelings, you can almost feel the additional weight of everything you're responsible for when you pick it up—the memories and soccer skills and boating talent and love affairs. People used to think that the soul resided in the heart, but when you pick up a brain, you are holding a person. It is impossible not to notice.

There is no way of knowing how much longer Al Gardner has left, but he has already made it clear where his brain will go when he dies. He wants it to go to research. Ideally the Mayo Clinic, which maintains a bank of brains ravaged by neurodegenerative diseases down in Jacksonville, Florida. But if that won't work out, cost-wise, a lab closer to home would be fine. Al made this wish clear to Fran a long time ago, when they were still talking wishes. PSP, this strange, rare illness, could be the door to a dozen brain diseases. Al wants his brain to have a shot at being the key.

For now, Fran can still take Al to doctor's appointments at Northern Westchester Hospital. She can bring him to his boxing class at the local gym. But when there's nothing else left to do for him, when she can't shred his chicken so he can swallow it or put on his sunglasses to go upstairs, she'll be able to help him give the physical embodiment of his soul to research. One day, she hopes, no one else will have to try so hard to remain optimistic, because the doctors and neuroscientists and engineers and philanthropists will have found something better: a cure.